Remarks

Status of the Claims

Claims 16-22 and 24-37 are pending, with claim 18 being withdrawn from consideration. Claims 1-15, 23 and 36 have been cancelled. Claim 16 has been amended and claim 37 is new. No new subject matter has been added.

Objections

Claims 19 and 20 were objected to under 37 C.F.R. 1.75(c) as being of improper dependent form for failing to further limit the subject matter of the previous claim. In response to this objection, Applicants have amended claim 16, from which claims 19 and 20 depend.

The Examiner noted that if claim 1, 16, or 34 are found to be allowable, claims 9, 23 and 36 will be objected to under 37 C.F.R. 1.75 as being substantial duplicates thereof. Applicants submit that claims 9, 23 and 36 have been cancelled herein.

Rejection of Claims 1-4, 9-17, 21-26, 30-34 and 36 Under 35 U.S.C. § 102(a) and § 102(e)

Reconsideration is respectfully requested of the rejection of claims 1-4, 9-17, 21-26, and 30-34 under 35 U.S.C. § 102(a) and § 102(e) as being anticipated by Sato et al. (U.S. Published Patent Application No. 2003/0092622). The rejection of claims 1-4, 9-15, 23 and 36 is moot in view of their cancellation.

Sato et al. is a U.S. application publication of an International Application, which was filed after November 29, 2000. However, the WIPO publication of the International Application (WO 01/64241) was published in Japanese, and therefore, U.S. 2003/0092622 does not have § 102(e) date and only qualifies as prior art under § 102(a). Accordingly, Applicants submit that the § 102(e) rejection is moot in view of the foregoing comments.

Claim 16 is directed to a stable pharmaceutical composition comprising erythropoietin and a peptide stabilizer selected from the group consisting of dipeptides, tripeptides,

tetrapeptides, pentapeptides, derivatives thereof and mixtures thereof, and wherein the composition is free of serum albumin.

Claim 34 is directed to a stable pharmaceutical composition comprising erythropoietin, a polyoxyalkylene sorbitan fatty acid ester, and a peptide stabilizer selected from the group consisting of Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-His, Gly-Asp, Gly-Ala, Ala-Gly, Ala-Ala, derivatives thereof and mixtures thereof, wherein the composition is free of serum albumin.

Sato et al. describe a protein formulation containing a stabilizer selected from tryptophan, a tryptophan derivative or a salt thereof. The addition of the stabilizer is said to promote long-term storage stability of the protein formulation. One of the proteins that may be stabilized using the method described by Sato et al. is erythropoietin. However, the only stabilizers that Sato et al. describe are tryptophan, tryptophan derivatives, and salts thereof. Paragraph [0047] lists a large number of salts and derivatives that can be used. As can be seen from that list, the stabilizer described by Sato et al. is always a single amino acid, i.e. tryptophan or a single amino acid derivative or salt, i.e. tryptophan derivative or salt. Sato et al. do not suggest or even mention the use of a peptide, such as a di- or tri-peptide for stabilization of protein formulations.

Furthermore, in paragraph [0043], Sato et al. state that their protein formulations are preferably substantially free from proteins such as human serum albumin. However, the present claims require that the stabilized protein formulations be free, and not only substantially free of serum albumin.

Claim 16 requires that a peptide stabilizer be selected from dipeptides, tripeptides, tetrapeptides, pentapeptides, derivatives thereof and mixtures thereof. Sato et al. describe only a single amino acid stabilizer, namely tryptophan or a derivative or salt thereof. Accordingly, claim 16 and its dependent claims 17-22 and 24-33 are novel over Sato et al.

Claim 34 requires that a stable pharmaceutical composition comprising erythropoietin be free of serum albumin and stabilized with one of the di- or tri-peptide stabilizers selected from Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-His, Gly-Asp, Gly-Ala, Ala-Gly, Ala-Ala, and

derivatives or mixtures thereof. Not only does Sato et al. fail to identify any dipeptide or tripepide stablizers, but none of the presently claimed di- and tri-peptides even contain tryptophan. Therefore, in view of the above comments, Applicants submit that claim 34 is novel over Sato et al. Furthermore, claim 35, which depends from claim 34 is novel over Sato et al. for the same reasons as the independent claim.

Rejection of Claims 3-7, 24-29 and 35 Under 35 U.S.C. §103(a)

Claims 3-7, 24-29 and 35 were rejected under 35 U.S.C. § 103(a) as being obvious over Sato et al. in view of WO 02/14356. The rejection of claims 3-7 is moot in view of their cancellation.

WO 02/14356 teaches the preparation of erythropoietin omega and methods of treatment using the same. The Office alleged that it would have been obvious to stabilize the erythropoietin omega of WO 02/14356 with a peptide stabilizer described by Sato et al. to preserve its therapeutic activities. With respect to Sato et al., Applicants again note that they only teach peptide stabilizers selected from tryptophan, tryptophan derivatives and salts, whereas the present claims require that a peptide stabilizer be selected from dipeptides, tripeptides, tetrapeptides, pentapeptides, derivatives thereof and mixtures thereof. Furthermore, WO 02/14356 does not teach or even mention that erythropoietin omega can be formulated using peptide stabilizers. Therefore, there would have been no motivation to combine the teachings of these two references, absent the hindsight analysis of the Applicants' disclosure. Furthermore, even if Sato et al. teachings were combined with the teachings of WO 02/14356, one skilled in the art would still not have arrived at the present invention, i.e., a stable pharmaceutical composition of erythropoietin comprising a peptide stabilizer selected from dipeptides, tripeptides, tetrapeptides, pentapeptides, derivatives thereof and mixtures thereof, which is free of serum albumin. Reconsideration of this rejection is respectfully requested.

Rejection of Claims 1 and 8-10 Under 35 U.S.C. §102(b)

Claims 1 and 8-10 were rejected under 35 U.S.C. 102(b) as being anticipated by Cormier et al. (U.S. Published Patent Application No. 2002/0058608). The rejection of these claims is moot in view of their cancellation.

Rejection of Claims 2-4, 11, 16, 17 and 19-24 Under 35 U.S.C. §103(a)

Claims 2-4, 11, 16, 17 and 19-24 were rejected under 35 U.S.C. § 103(a) as being obvious over Cormier et al. The rejection of claims 2-4, 11 and 23 is moot in view of their cancellation.

Cormier et al. teach a buffered aqueous formulation for transdermal electrotransport delivery, which comprises a therapeutic agent buffered with a dipeptide buffer. According to Cormier et al., a therapeutic agent formulated in this manner can be selected from a vast number of different compounds, ranging from antibiotics, antiviral agents, anesthetics and antimigraine agents to proteins, peptides, hormones and muscle relaxants (see paragraph [0033]). The list of proteins and peptides that are said to be applicable embraces **over 90 agents**, including erythropoietin (see paragraph [0034]). However, Cormier et al. only exemplified formulations of human growth hormone, synthetic radiolabeled decapeptide (DECAD), and small molecular weight drug-like compounds such as trimethylammonium bromide (TMAB) and sodium methanesulfate (SMS) in the working examples of the patent.

It is said that it would have been obvious to administer EPO using the Gly-His buffer of Cromier et al. because the reference discloses that EPO is a protein which can be usefully administered in their formulations.

Claim 16 relates to a stable pharmaceutical composition comprising erythropoietin and a peptide stabilizer selected from the group consisting of dipeptides, tripeptides, tetrapeptides, pentapeptides, derivatives thereof and mixtures thereof, and wherein the composition is free of serum albumin. Cormier et al. do not teach a buffered aqueous formulation containing erythropoietin. At most, they would invite one skilled in the art to try formulating erythropoietin, in addition to over 90 other proteins and peptides, with a dipeptide buffer. Based on the

teachings of Cormier et al., one skilled in the art would not have been motivated to formulate erythropoietin in a pharmaceutical composition comprising a peptide stabilizer selected from the group consisting of dipeptides, tripeptides, tetrapeptides, pentapeptides, derivatives thereof and mixtures thereof, wherein the composition is free of serum albumin. Moreover, based on the large number of proteins listed in Cormier et al., and only one example showing formulation of human growth hormone, one skilled in the art would have had no reasonable expectation of success in formulating erythropoietin with a peptide stabilizer in order to produce a stable pharmaceutical composition.

With respect to peptides taught by Cormier et al., the preferred dipeptide buffer is Gly-His. The following paragraph of Cormier et al. is also of note:

> [0012] Although histidine has been used to buffer protein formulations (WO 93/12812), the use of histidine to buffer electrotransport drug formulations is **problematic** due to the poor chemical stability of histidine in aqueous solutions. Water is by far the most preferred liquid solvent for electrotransport drug formulations due to its excellent biocompatability when in contact with skin. The aqueous stability of histidine is **so poor** that the formulations are **not able** to achieve the **minimum stable shelf life** required by drug regulatory agencies. (Emphasis added.)

Thus, it can be seen that a peptide buffer that works well for electrotransport drug formulations may not work at all with regular protein formulations and vice versa. Accordingly, one skilled in the art having knowledge of the teachings of Cormier et al. would not expect those teachings to apply to a pharmaceutical formulation comprising erythropoietin. Applicants also note that while Cormier et al. do not mention serum albumin, they do not exclude it from their formulations either. Accordingly, Applicants submit that claim 16 and claims 17-24, which depend therefrom are non-obvious over Cormier et al., and respectfully request withdrawal of the rejection.

With respect to the new claim 37, Applicants note that it relates to a stable pharmaceutical composition comprising erythropoietin and a peptide stabilizer, wherein the composition is free of serum albumin and is for parenteral administration. Thus, this claim is not

obvious over Cormier et al.'s transdermal formulations which would not suggest how a parenteral formulation should be prepared and stabilized.

Rejection of Claims 3-7 and 24-29 Under 35 U.S.C. § 103(a)

Claims 3-7 and 24-29 were rejected under 35 U.S.C. § 103(a) as being obvious over Cormier et al. in view of WO 02/14356. The rejection of claims 3-7 is moot in view of their cancellation.

The Examiner alleged that it would have been obvious to formulate the erythropoietin omega of WO 02/14356 in the compositions of Cormier et al. because it would be desirable to administer erythropoietin omega iontophoretically and Cormier et al. teach administration of a wide range of proteins. Firstly, Applicants refer to the above sections, which discuss the deficiencies of Cormier et al. disclosure. Secondly, Applicants note that erythropoietin is generally administered intravenously, subcutaneously, or via infusion due to the stability and size issues experienced with the administration of a large number of proteins. Thirdly, iontophoretic administration is still minimally used due to the low permeability of human skin, which makes the transport of large proteins difficult. Cormier et al. do not teach the transdermal administration of erythropoietin, but only include erythropoietin in a long list of proteins that may be administered iontophoretically. WO 02/14356 does not suggest transdermal administration of erythropoietin or desirability for such transport. Finally, WO 02/14356 does not teach or even mention that erythropoietin omega can be formulated using peptide stabilizers. Therefore, there would have been no motivation to combine the teachings of these two references, absent the hindsight analysis of the Applicants' disclosure. Thus, Applicants submit that claims 24-29 are non-obvious over Cormier et al. in view of WO 02/14356.

Rejection of Claims 12-15 Under 35 U.S.C. § 103(a)

Claims 12-15 are rejected under 35 U.S.C. §103(a) as being obvious over Cormier et al. in view of Holladay et al. (U.S. Patent No. 6,328,728). Claims 12-15 are cancelled so this rejection is moot.

Rejection of Claims 30-34 and 36 Under 35 U.S.C. § 103(a)

Claims 30-34 and 36 were rejected under 35 U.S.C. §103(a) as being obvious over Cormier et al. in view of Holladay et al. Claim 36 has been cancelled, and its rejection is moot.

Cormier et al. teachings are discussed above, and are not repeated in this section. It is said that it would have been obvious to one of ordinary skill in the art to include a surfactant of Holladay et al. in Cormier et al. compositions to increase the flux or decrease biodegradation of proteins during electrotransport delivery.

Holladay et al. teach a method of enhancing electrotransport delivery of an active agent, such as a protein in the presence of at least one electrotransport enhancer selected from nonionic surfactants, zwitterionic surfactants lacking a net charge, and mixtures thereof, such as a polyoxyalkylene sorbitan fatty acid ester. The deficiencies of Cormier et al. cannot be cured by the teachings of Holladay et al. The combination of references would not have motivated one skilled in the art to formulate erythropoietin in a pharmaceutical composition comprising a peptide stabilizer and surfactant as claimed.

Without reference to the teaching of the instant invention, one would not have had a reasonable expectation of success of achieving stabilization of erythropoietin with peptide stabilizers without the addition of serum albumin. Therefore, the combination of references, when viewed by one skilled in the art, would at best have been obvious to try, which without reasonable expectation of success is an improper standard for rejection under 35 U.S.C. §103(a). The courts have consistently held that the test for a prima facie case of obviousness is not

whether an invention is obvious to try.[1] Instead, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to combine the references, and there must be some reasonable expectation of success. The Office has not met this legal standard.

A determination of obviousness requires evidence which establishes not merely what one skilled in the art might be led to attempt, but that he have a reasonable basis in the art for expecting to succeed. "The invention must be viewed not with the blueprint drawn by the inventor, but in the state of the art as it existed at that time."[2] Moreover, it is improper to use the claims as a frame from which individual naked parts of separate prior art references may be employed as a mosaic to recreate the claimed invention.[3] The cited art does not suggest the claimed combination of features. The law requires not merely a rational hope, but a concrete basis to expect success. Applicants therefore respectfully submit that the cited art, singly or in combination, provides no teaching, motivation or expectation of success with regard to the claimed composition.

Rejection of Claim 35 Under 35 U.S.C. § 103(a)

Claim 35 was rejected under 35 U.S.C. §103(a) as being obvious over Cormier et al. in view of WO 02/14356 and Holladay et al. It is said that it would have been obvious to one of ordinary skill to include Holladay's surfactant in Cormier's compositions as modified to include the EPO omega of WO 02/14356 to increase the flux or decrease biodegradation of proteins during electrotransport delivery.

Claim 35 is directed to a stable pharmaceutical composition comprising erythropoietin omega, a polyoxyalkylene sorbitan fatty acid ester, and a peptide stabilizer selected from the

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[1]See *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1680-81 (Fed. Cir. 1988).

[2]quoting *Interconnect Planning Corp. v. Feil* 227 USPQ 543 at 547 (Fed. Cir. 1985).

[3]Id. at 551.

group consisting of Gly-Gly, Gly-Gly-Gly, Gly-Tyr, Gly-Phe, Gly-His, Gly-Asp, Gly-Ala, Ala-Gly, Ala-Ala, derivatives thereof and mixtures thereof, wherein the composition is free of serum albumin.

The deficiencies of Cormier et al., WO 02/14356 and Holladay et al. teachings are discussed above. More specifically, Cormier et al. show only one example of the aqueous buffered formulation of a protein, i.e., human growth hormone, and Holladay et al. teach a method of enhancing electrotransport delivery of an active agent in the presence of at least one electrotransport enhancer such as a non-ionic surfactant, zwitterionic surfactant lacking a net charge, or a mixture thereof. WO 02/14356 does not teach or even mention that erythropoietin omega can be formulated using peptide stabilizers or that it may be desirable to administer erythropoietin iontophoretically. Without reference to the teaching of the instant invention, one would not have had any motivation to formulate the claimed composition and would not have had a reasonable expectation of success of achieving stabilization of erythropoietin with peptide stabilizers without the addition of serum albumin.

Rejection of Claims 1 and 9-15 Under 35 U.S.C. § 103(a)

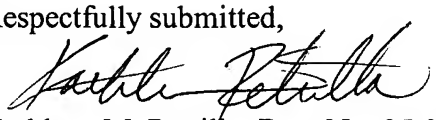
Claims 1 and 9-15 were rejected under 35 U.S.C. §103(a) as being obvious over Bjorn et al. (U.S. Published Patent Application No. 2003/0162711). Claims 1 and 9-15 are cancelled and the rejection is moot in view thereof.

Conclusion

In view of the foregoing comments, Applicants respectfully request entry of the amendments and solicit allowance of the claims.

Applicants enclose a check in the amount of $120.00 for a one month extension of time. The Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,



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